REMARKS

Claims 1-23 are pending in the application. Claims 2-3 are objected to. Claims 1 and 4-23 are rejected. Claims 1, 2, 3, 4, and 23 have been amended to more clearly define Applicants' invention. No new matter has been added to the application.

Summary of Claim Amendments

Claims 1 and 23 have been amended to exclude Asn-Gly-Arg, or Gly-Ser-Leu.

Claims 2 and 3 have been amended to include *trans*-4-hydroxy-proline (t4Hyp) as a member of the third amino acid of the antiangiogenic tripeptides. Support for these amendments can be found in Example 5 (Table 4) and Figure 5 where the tripeptide S-N-t4Hyp exhibited significant antiangiogenic activity.

Claim 4 has been amended to specify that the tripeptide is not capped with an amino acid or peptide, and Claim 23 had been amended to exclude peptides as capping agents.

Objection under 37 CFR 1.75(c)

Claim 4 is rejected (objected) under 37 CFR 1.75(c) for failing to claim subject matter that narrows the scope of Claim 1. The Examiner believes that Claim 4 could include a tripeptide which is capped by amino acids or by another peptide; thereby increasing the scope of Claim 4 beyond the scope of Claim 1.

The Applicants have amended Claim 4. Specifically, amino acids and polypeptides are excluded as capping agents. Additionally, Claim 23 has been amended to remove peptides from the list of capping compounds.

Rejection under 35 U.S.C. §102(a)

Claims 1, 4 and 7 are rejected under 35 U.S.C. §102(a) as being anticipated by Brown et. al. (*Annals of Surgical Oncology* V7, N10 (Dec.), p743-749 (2000)). The Examiner asserts that Brown et al. teach antiangiogenic tripeptides of the formula RGD and NGR (p.744, Col. 1, 3rd para. And Figure 1). It is believed by the Examiner that Brown et al. teach all of the elements of claims 1, 4, and 7 and that these claims are anticipated under 35 U.S.C. 102(a). The Applicants respectfully traverse in rebuttal to this rejection. However, Applicants' remarks herein should not be construed as an admission or acknowledgement that Brown et

al. is prior art against the present application or that the present invention was described in a printed publication prior to Applicants' invention thereof under 35 U.S.C. § 102(a).

Brown et al. teach several tripeptides of the formula RGD, NGR, and GSL which have been shown to bind to angiogenic epithelium (Page 744, Figure 1). The specific utility of the Brown tripeptides is targeting of therapeutic agents to endothelial cells. Specifically, Brown et al state on page 748, column 2, 3rd paragraph, "Aside from the therapeutic targeting of the tumor vasculature, peptides that will specifically bind to tumor endothelium can be used as a possible diagnostic tool." In contrast, Applicants illustrate how the tripeptides of the present invention actually have antiangiogenic properties, which, Applicants assert, is distinct from binding activity to epithelium cells.. Further, we note that Claim 1 was previously amended to specifically exclude tripeptides of the formula RGD ("Arg-Gly-Asp"), and that Claims 1 and 2 are currently amended to specifically exclude tripeptides of the formula RGD, NGR, and GSL. Based upon these comments and amendments, Applicants' respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. §103(a)

Claims 1, 4-17, and 20-23 are further rejected under 35 U.S.C. §103(a) as being unpatentable over Blaschuk et al. (US 6,031,072). The Examiner states the Blaschuk et al. teach a small peptide of four or more amino acids comprising the sequence XHAV, wherein X may be any amino acid (col. 3, lines 14-17), that inhibits angiogenesis in a mammal (col. 2, lines 66-67 to col. 3, lines 1-10 and col. 3, lines 60-64) or administered to treat rheumatoid arthritis (col. 28, lines 20-23) and wherein the peptides may be capped by an acetyl group and a C-terminal amide group (col. 3, lines 20-30), linked in a composition to a drug and adminstered to an inflamed tissue of a tumor to inhibit angiogenesis (col. 4, lines 5-10 and for inflamed tissue see col. 20, lines 10-30), administered to a mammal to inhibit angiogenesis (col. 3, lines 60-64) via a pharmaceutically acceptable medium, namely, a skin patch (col. 5, lines 1-2) or via biodegradable polymers (col. 17, lines 1-10) and in combination with an antibiotic (col. 18, lines 40-62) and in surgery or chemotherapy (col. 20, lines 10-30). The Examiner further states that Blaschuk et al. do not teach a tripeptide but that given that Blaschuk et al. teach that a tripeptide HAV within a larger peptide is responsible for the antiangiogenic properties of the peptide, it would have been obvious to one of ordinary skill in the art at the time of the invention by the applicant to administer the tripeptide along to treat angiogenesis and to administer it via any well-known delivery method such as skin

patches, osmotic pumps, orally, or nasally, for example. Applicants respectfully traverse. However, Applicants' remarks should not be construed as an admission or acknowledgement that Blaschuk et al. is prior art against Applicants' invention under 35 U.S.C. § 103. It is noted that the present application claims priority to 16 February, 2001, and that the date of publication of Blaschuk et al. is 29 February 2000.

Applicants first wish to emphasize that Blaschuk et al. (US 6,031,072) does not teach antiangiogenic tripeptides; rather, Blaschuk et al. teach cyclic peptides comprising a cadherin cell adhesion recognition sequence HVA (His-Ala-Val). The compounds recited in Blaschuk et al. are specifically limited to cyclic peptides having a sequence longer than the tripeptides of the present invention. The Blaschuk cyclic peptides include a cadherin cell adhesion recognition sequence (CAR), such as HAV, within the larger cyclic compound. Specifically, Blaschuk et al. state "In addition to the CAR sequence(s), cyclic peptides generally comprise at least one additional residue, such that the size of the cyclic peptide ring ranges from 4 to about 15 residues, preferably from 5 to 10 residues" (Col 8., lines 42-45). In further contrast to Blaschuk, the present invention teaches antiangiogenic tripeptides. Applicants assert that Blaschuk et al. does not teach that the CAR sequence, HAV, has antiangiogenic properties, in fact, Blaschuk could be construed as a negative teaching in this regard. Blaschuk et al. disclose in Example 5 (Col. 35., lines 34-40) "The cyclic peptides H-CHAVC-NH2, with the N-terminal blocking group removed, inhibited angiogenesis by 27%, 34%, and 35% at concentrations of 3, 17, and 33 μg/mesh, respectively. The cyclic peptides N-Ac-CHAVSC-NH2 was found to be inactive in this assay". Based upon this teaching in Blaschuk, Applicants respectfully assert it could be concluded that the HAV sequence is not responsible for the reported antiangiogenesis activity since one of the sequences In Example 5 containing HAV exhibited no antiangiogenic activity. Additionally, the Examiner states on page 4 of the present office action:

> "Given that Blaschuk et al. teach that the tripeptide HAV within a larger peptide is responsible for the antiangiogenic properties of the peptide, it would have been obvious to one of ordinary skill in the art at the time of the invention by the applicant to administer the tripeptide along to treat angiogenesis and to administer it via any well-known delivery method such as skin patches, osmotic pumps, orally, or nasally, for example (present claim 16)."

The Applicants respectfully disagree with the Examiner. As noted above, Blaschuk does not unambiguously teach that an HAV tripeptide has antiangiogenesis activity. The HAV sequence is disclosed by Blaschuk to be a cadherin cell adhesion recognition sequence. The ability of a compound to bind to cadherin does not necessarily suggest antiangiogenesis activity. Additionally, we again note that the teachings of Blaschuk are limited to compounds longer than the tripeptides of the present invention.

Based upon the above discussion, Applicants respectfully assert that it would not have been obvious to one of ordinary skill in the art, based upon Blaschuk, to administer any tripeptide for the purpose of inhibiting angiogenesis as claimed by Applicants. The Applicants further note that they have amended Claim 4 to limit the scope of the capping compounds to exclude amino acids and peptides in order to clearly define the invention as being limited to antiangiogenic tripeptides.

Claims 1, 9, 18, and 19 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Blaschuk et al. as applied to claims 1 and 9 above, and further in view of Wickam et al. (Journal of Virology, Vol. 71, No. 11, Nov. 1997, pp.- 8221-8229). The Examiner states that Wickam et al. teach a method of incorporation of an angiogenesis-inhibitory tripeptide sequence into an adenovirus (p. 8221, col. 1, 1st paragraph) and nucleic acids (p. 8222, col. 2, last paragraph) and that as recombinantly produced proteins carry the advantage of being more pure and often cheaper than purified proteins, it would have been obvious to one of ordinary skill in the art at the time of the invention by the applicant to administer the angiogenesis-inhibitory peptide to tissue via encoding nucleic acid and incorporation into a vector, adenovirus, or DNA. Thus, the Examiner states, the claimed invention was *prima facie* obvious to make and use at the time the claimed invention was made. Applicants respectfully traverse.

The teachings of Blaschuk et al. (US 6,031,072) have been discussed previously. Wickham et al. additionally teach the use of the RGD binding motif to target adenovirus attachment to a target tissue. The Applicants first respectfully remind the Examiner that the RGD amino acid sequence was specifically removed from the scope of Claim 1 in response to the prior office action.

It should be noted that Wickham et al. merely teach that the RGD motif is a high-affinity α_v integrin binding motif. The adenovirus fiber gene was modified to express an 11 amino acid integrin binding sequence which contained the RGD motif. The 11-mer was used to target adenovius particles to tissues expressing α_v integrin. Wickham et al. note on page 8244, column 2, that binding motifs shorter than the above mentioned 11-mer construct were incompatible for the correct

folding of the modified fiber protein. Additionally, Wickham et al. note that RGD binding motifs having lengths of 32 amino acid did not target the adenovirus particles to the target receptors. In sum, Applicants believe that Wickham et al. do not teach or suggest antiangiogenic tripeptides. Further, the specific RGD sequence cited by the Examiner as disclosed in Wickham was previously removed from the scope of Applicants' Claim 1. Based upon these comments, Applicants do not believe their claimed invention could be obvious over the teachings of Blaschuk in view of Wickam, and withdrawal of this rejection is respectfully requested.

In light of the amendments to the Claims entered by Applicants and the technical arguments presented herein, Applicants respectfully request that the Examiner withdraw all present objections and rejections. It is believed a complete response has been made to the Official Action dated 14 August 2003, and that the application stands in condition for allowance. Such action is respectfully solicited. If further communication with Applicants' attorney would be helpful in advancing this application to allowance, the Examiner is invited to contact Applicants' attorney at the telephone number provided below.

Respectfully submitted,

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Dated: December 24, '03